Editorial

Mood Stabilisers, but for Lithium, are not stabilizing Moods!
Bipolar Disorders: Clinical conundrums 2

Treatment of Bipolar Disorders (BD) needs a therapeutic shift; demands a soul searching introspection. Therapeutic shift may have to be radical; a conceptual shift. Not simple, but a Transformative conceptual shift!

In 1949, when John Cade announced the usefulness of Lithium in patients with Mania, he might not have foreseen the change of course the psychiatric discipline is to make with regards to the treatment of psychiatric disorders. Even before the advent of neuroleptic agents, Lithium strengthened the biological theory of mental illness, credited for "Pharmacological Dissection of Psychoses", and continues to do so. Many pharmacological agents for episode management and prophylaxis have later appeared which have changed the therapeutic landscape of bipolar disorder (BD) management to a great extent. However these advances do not seem to guarantee the expected therapeutic relief, as succinctly summarised by Gary Sachs "Clinical Efficacy studies expand the armamentarium of evidence based treatments for BD…but… population of patients with inadequate response to these treatments seem to grow ever larger…"

In this article we make an attempt to discuss the problems in the concept and management of BD from a clinical perspective. We want to re emphasize the fact that mood disorders are one group of psychiatric disorders with excellent to good prognosis, 50% of the course in a state of total euthymia, as has been well described in the long term follow up studies of Judd,[1] Angst[2] and Soloman *et al*.[3] Martino *et al*., 2017[4] have shown, in patients with a mean follow up of about 77 months, that preliminary results do not support the hypothesis that functional outcome deteriorates over the course of illness in BD. There is a need to understand the chronicity of BD being different from the chronicity of say, Schizophrenia, OCD, Diabetes or Hypertension. **BD is unique in that significant group of patients remain in the asymptomatic state of euthymia for extended periods of time without any intervention, either pharmacological or psychological. The descriptions of "chronicity" in the current literature on BD coupled with "mood stabilization from the very first episode extending for unknown years…." seem to totally undermine the "Recovery" and "Good Prognosis" concept of the disorder!**

In the management of BD there are three goals for a clinician:

1. **Reduce current episode morbidity – clinician "Facilitates" the natural course of "Recovery"**
2. **Prevent future episode morbidity – clinician "Antagonizes" the natural course of "Recurrence"**
3. **Prevent suicidal mortality**

ACUTE EPISODE MANAGEMENT - MANIA

Mania is the quintessential defining syndrome of the bipolar disorder, though depression is the "longer, morbid and mortal" episode! Last 3 decades have witnessed a popular discourse within the psychiatric guild which reinterpreted mania in several new ways; hypomania, soft bipolar (including Akiskal's classification), subsyndromal hypomania, bipolar spectrum….

Clinician has three options for the management of acute manic episode:

1. Antipsychotic alone (Monotherapy)
2. Mood stabiliser alone (Monotherpay)
3. Mood stabiliser along with Antipsychotic (Polypharmacy)

Clinical experience reveals that monotherpay with antipsychotic alone gives as satisfactory a result as the Polypharmacy of mood stabiliser with antipsychotic for recovery of acute manic episode!

ACUTE EPISODE MANAGEMENT - DEPRESSION

Management of depressive episode is riddled with its own problems. Antidepressants are considered "mood destabilisers" and recommended against in many treatment guidelines for fear of lack of efficacy and switch induction; when used guidance for dosage and duration of medication is highly restrictive! Do we have enough evidence to arrive at this conclusion? Clinician's concern in the treatment of bipolar depression is not just about

the mood state but also about preventing suicide, rightly so. Suicidal attempts are 60 times more in the depressive phase compared to euthymic state![5]. What level of evidence is available regarding suicide prevention efficacy of Quetiapine or Lurasidone? Effective pharmacotherapy for prophylaxis of depressive episodes, in spite of lithium and Lamotrigine, seems elusive!

MAINTENANCE THERAPY - MOOD STABILIZATION/PROPHYLAXIS

As the conceptual notions changed, so did the management of the disorder. Evidence based algorithms dictate initiation of "mood stabilization" irrespective of bipolar type, episode phase and severity; the well-intentioned goal being reducing chronicity, and minimizing neurobiological sequelae. Polypharmacy is supported as being routinely helpful and in some sense even necessary! There are about 24 therapeutic guidelines for bipolar disorder and every single algorithm goads the clinician to initiate mood stabiliser from day one! Treatment of BD without "mood stabiliser" is unacademic, unethical, rather unthinkable, they dictate! Yes, sounds a logical step. But the hypothesis to be tested is "whether these mood stabilisers really do mood stabilization" in the true meaning of prevention of next episode! Does not seem so! Our clinical experience reveals that in the majority of patients with BD it is the natural course of illness that dictates the long term outcome, modified a little, if at all, by the mood stabilisers![6]. A distortion, someone may scream; but the truth of the reality stares hard at the clinician who maintains the follow up documentation! The practicing clinician squirms uneasily everyday when patient after another patient relapses while on good therapeutic dose of "mood stabilisers"; drugs with doubtful efficacy but with loads of adverse events!

Valproate – 1. Net work meta analysis in 2015 by Yildiz *et al*.[7] showed that valproate has least efficacy in the treatment of acute mania when compared to 12 other commonly used drugs. 2. Varquez *et al*. 2015[8] has shown that valproate and anticonvulsant medications are almost equal to placebo in the prevention of recurrences.

Lithium is backed-up by research evidence with regards to its anti-manic properties and prophylactic efficacy in preventing manic relapses, but less effect in depressive episode management and prophylaxis. Narrow therapeutic index and high dropout rate (about 50%) plague use of Lithium. Therapeutically effective serum lithium levels range from 0.6 – 1.2 meq/ltre, the trough serum levels. It used to be the standard practice to prescribe lithium twice daily and measure the serum level 12 hours after the last dose. With the introduction of slow release preparations it is now a widely accepted practice to prescribe lithium medication as once a day dosage. The true trough level remains the one measured at 24 hours from the last dose! Are we following this when we order the timing of blood sample for lithium level estimations?[9]. Anne Berghofer *et al*., 2013[10] in a prospective 20 year follow up did not find lowering of Morbidity Index with lithium. Lithium tended to be generally better than the other active comparators, with small statistical variations between the results[11].

The evidence for Lamotrigine, the mood stabiliser for depressive episodes, is conflicting and the drug despite its safe adverse effect profile, do not find favor with clinicians!

Evidence for prophylaxis in patients with rapid cycling and ultra rapid cycling is too well known for its lack of efficacy!

RELEVANT BIPOLAR RESEARCH FOR DISCUSSION

1. Both Jorvi's longitudinal study [Figure 1] and Judd's study [Figure 2] highlight the excellent prognosis of BD with euthymic states measuring to around 50% of the course.
2. Bipolar disorder over the last 25 years had lot of progress in terms of hastening the episode recovery in acute state from an average of 6 months to one month. Fruits of pharmacological advances in acute episode management! [Figure 3]
3. Heterogeneity in the frequency and number of episodes, and unpredictability of occurrence of next episode is an accepted norm in patients with BD. Clinical experience highlights two events that

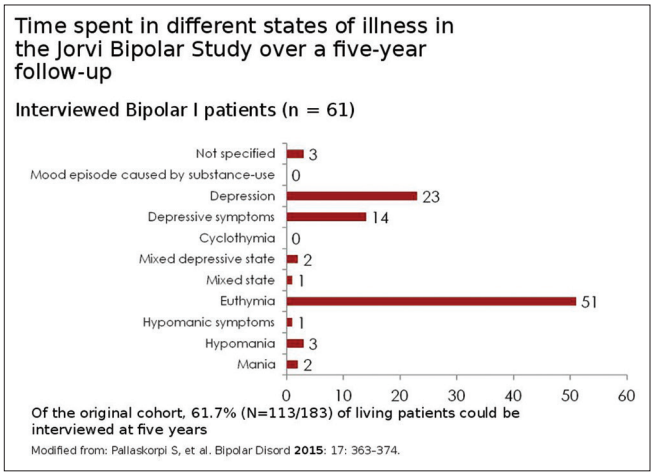

Figure 1: Time spent in different states of illness

have high predictive value for the occurrence of next mood episode. **1. Postpartum**: In a female patient with established diagnosis of BD, the almost certain predictor for the onset of next episode is the post partum; rather the one and only certain precipitating factor for relapse of a mood episode! Not having the future post partum period may not assure of a non relapse, but the next postpartum period can offer crystal gazing prediction of a certain relapse! What could be the "hormonal disequilibrium" that precipitates the episode? Do we have a mood stabiliser that can prevent this relapse? **2. Season** – It is an observed fact over a decade that the relapse of manic episodes is predictably higher in the months of April-May and again in Oct-Nov, at least at our bipolar clinic! This happens irrespective of the compliance of the pharmacotherapy! Do other clinicians share the same experience and is there a role for seasonal prophylaxis? Do we have a mood stabiliser, which assures the patient of prophylaxis when we start the medication a good two month prior to these seasons?[12]

4. Recurrence rates are lowest in the groups which were either on antipsychotic agents alone or on a combination of mood stabilizer and antipsychotic agents, compared to mood stabilizers alone (i.e., Lithium, Valproate, Carbamazepine). [Figure 4]
5. In naturalistic studies with substantial prospective follow up to 20 years with good frequency of follow up i.e. 7-8 visits per years in 346 patients showed that, even when Serum Lithium level was above 0.5 mmol/L, Lithium use did not bring about a reduction in the morbidity index, which is calculated based on time spent in morbidity which either requires out-patient or in-patient care [Figure 5]. Hayes J *et al*. 2011 showed the changing trend of prescription of lithium in UK [Figure 6]
6. Miura T *et al*., Lancet 2014[13] - A systematic review and network Meta-analysis - 33 RCTs…6846 participants…1970 to 2012…17 treatments assessed…Participants assigned to Any Assessed Treatment had a significantly lower risk of mood relapse or recurrence compared with placebo – "Any intervention is better than placebo".

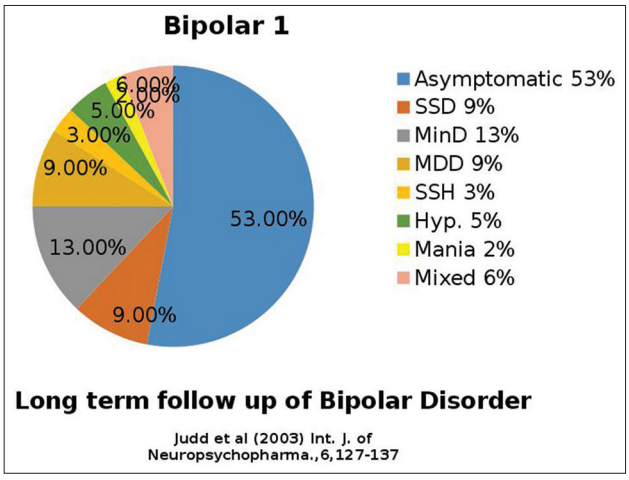

Figure 2: Long-term follow-up of bipolar disorder

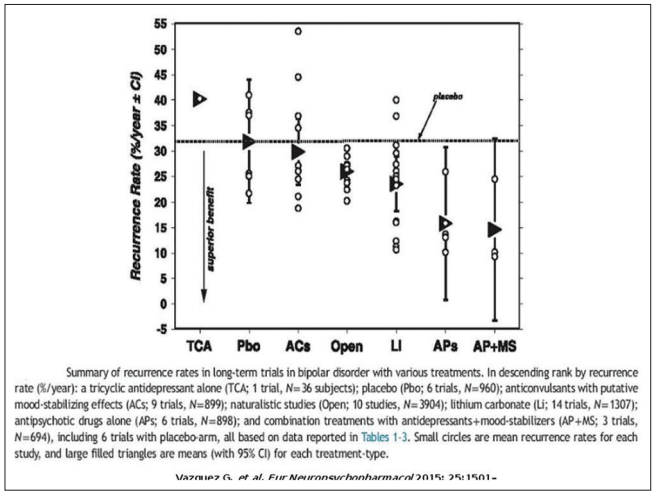

Figure 4: Summary of recurrence rates in long-term trials in bipolar disorder

	1875 - 1924	1994 - 2005
Females	60%	60%
Average age of First Admission	32	31
Average length of hospital stay for one episode	6 Months. **Almost all patients went home well.**	1 Month

Bipolar Disorders, Clinical and Neurobiological Foundations By
Lakshmi N.Yatham and Mario Maj, Wiley-Blackwell, 2010

Figure 3: North West wales asylum story

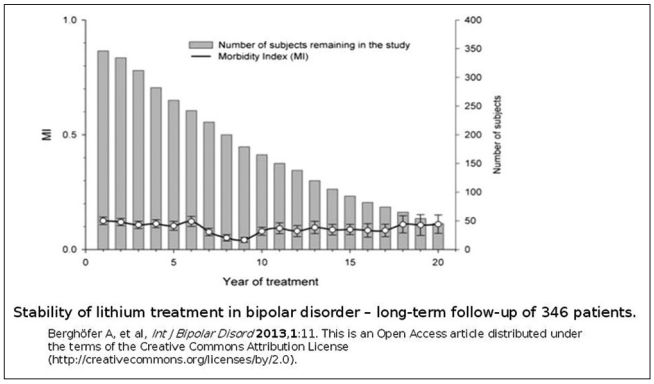

Figure 5: Morbidity index

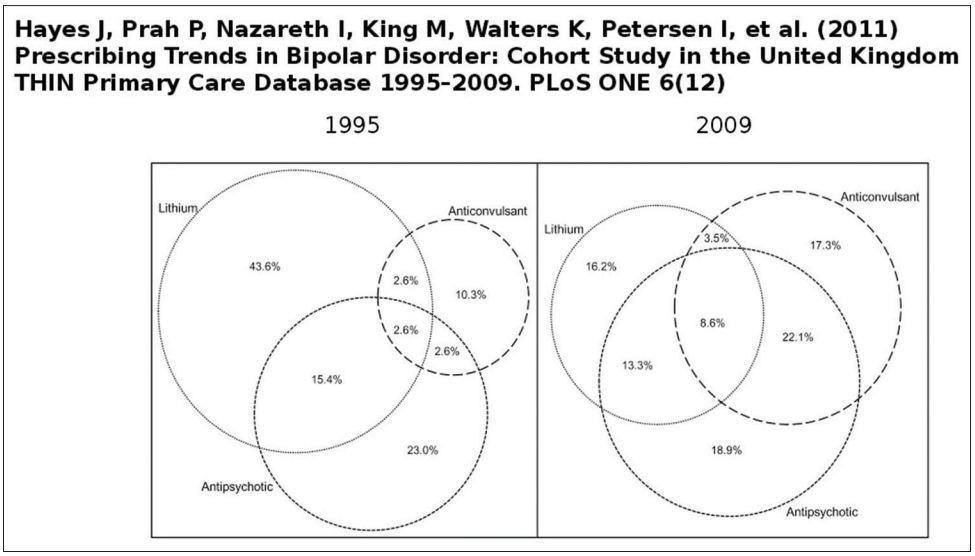

Figure 6: Prescribing trends in bipolar disorder

7. Is it a post 12hour or 24 hour blood sample for serum lithium estimation when the dosing is on a once a day basis?

SOME UNANSWERED QUESTIONS

1. Excellent prognosis with certainty of recovery from acute episode is a well accepted fact. Natural course of BD offers a cushion of euthymic state for 50% of duration. With this background, are we prematurely advising every patient to be started on mood stabilisers, most of them with doubtful efficacy, from day one of the disorder! Prophylaxis is required, no doubt, but may be for the specific group with high morbidity in severity and frequency. Dictum of prophylaxis from the very first day one needs a revisit! **Reasons – 1. It undermines the positive outlook and excellent prognosis of BD 2. Unwarranted long time medication with drugs of doubtful efficacy, especially when the common age of onset of BD is 15-25 years!**
2. Can we work towards monotherapy over polypharmacy in the management of Bipolar disorder!
3. Every clinician knows that the tough part in the management of bipolar disorder is the depressive episode (3 times the duration of manic episodes). What do we offer our patients now - Highly polarized opinions in the acute depression treatment and low evidence data for long term depression prophylaxis!
4. When the Bipolar II disorder treatment guidelines are formulated largely by extrapolating Bipolar I disorder data, should we use similar treatment methods in both? Judd studied that for every 37 days suffered in depressive phase only one day is spent in a hypomanic phase (which doesn't have significant socio-occupational dysfunction). **Are we doing it right in choosing mood stabilisers, for this Bipolar II group, with unproven efficacy both in the acute treatment of depression and also in prophylaxis of depressive episodes?**

The clinician demands a Transformative Conceptual Therapeutic Shift:

- Reinvent and Emphasise GOOD PROGNOSIS of BD
- Recognise HETEROGENEITY of Bipolar Disorder - Both cross sectional and longitudinal course
- Prophylaxis to be decided on Individual/specific "Bipolar group" basis
- MINIMISE POLYPHARMACY
- Consensus on management of Bipolar Depression, Acute and Prophylaxis
- Replace the term "Mood Stabiliser" with Prophylaxis
- Therapeutic need to initiate Prophylaxis in the First episode
- Effective prophylaxis for Postpartum and Seasonal mood episodes.

CASE REPORTS of Individual patient's long term follow up may provide more valid indicators of prophylaxis than RCT.

John Cade's research on lithium is Case Report based!!!

CONCLUDING THOUGHTS

In BD, both the recovery and recurrence are a rule. Discussion on the current therapeutic scene is not meant to project pessimism but to help us to think

clearly about various treatment outcomes and possibilities that we have as clinicians. We propose that BD has to be sub-grouped based on characteristics like course, pattern of relapses, family history, treatment response etc. We think that the available generalized guidelines do not provide us with a nuanced way of treating the individual patient that we see in our clinic every day. We need to devise mechanisms to tailor the treatment.

These two editorials (Volume 39, issues 4 and 5) on clinical problems with bipolar disorder are made based on the database, which was maintained over last decade at Asha bipolar clinic (ABC). The questions are raised as the need for constructive criticism and self-examination within the psychiatric guild was recognized, so that we can answer them with a view to stand up to the responsibility to help a person with bipolar disorder live better. Our point is to find ways to convert research efficacy into everyday effectiveness by combining empirical evidence with clinical expertise.

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